

⑫

EUROPEAN PATENT APPLICATION

⑰ Application number: 84300616.4

⑤① Int. Cl.³: **C 07 D 501/24**
//A61K31/545

⑱ Date of filing: 01.02.84

③① Priority: 07.02.83 US 464223

④③ Date of publication of application:
12.09.84 Bulletin 84/37

⑧④ Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

⑦① Applicant: **PFIZER INC.**
235 East 42nd Street
New York, N.Y. 10017(US)

⑦② Inventor: **O'Brien, Daniel Joseph**
2, Box 565
Canterbury Connecticut(US)

⑦④ Representative: **Graham, Philip Colin Christison et al,**
Pfizer Limited Ramsgate Road
Sandwich, Kent CT13 9NJ(GB)

⑤④ Process for the manufacture of highly crystalline sodium cefoperazone.

⑤⑦ A process for the preparation of highly crystalline sodium cefoperazone comprising the controlled addition of acetone to a water/acetone/sodium cefoperazone solution and subsequently separating the resulting crystalline sodium cefoperazone.

PROCESS FOR THE MANUFACTURE OF HIGHLY
CRYSTALLINE SODIUM CEFOPERAZONE

This invention relates to a novel, convenient and economic process for producing sodium cefoperazone. More particularly, it relates to the production of highly crystalline sodium cefoperazone.

Cefoperazone is a broad spectrum beta-lactam antibiotic usually administered parenterally as the sodium salt, which is provided by the available procedures (British Patent Specification 1, 508, 071) as an amorphous solid.

Amorphous compounds are, in general less desirable than are crystalline forms thereof, from the standpoint of preparation, storage and use. A crystalline compound is generally considerably more stable than an amorphous form of the compound, and resists decomposition and discoloration. For pharmaceutical use, it is much easier to prepare dosage forms from crystalline compounds than from those in amorphous form. Finally, amorphous compounds are frequently more hygroscopic than those in crystalline form.

A relatively simple, inexpensive process has now been discovered to obtain highly crystalline sodium cefoperazone essentially free of residual organic solvents, comprising the steps of combining a water/acetone/cefoperazone solution containing 1.0-1.5 parts of water by volume, 2.0-5.0 parts of acetone by volume, and 1 part of sodium cefoperazone by weight.

with sufficient acetone to provide a water/acetone solution containing from about 14% to 17% water v/v, at about 5 to 25°C with a preferred temperature of 18-25°C; adding sufficient acetone to the resulting slurry at said temperature to provide a water/acetone solution containing from about 3% to 5% water v/v, based on acetone level; and separating the resulting crystalline sodium cefoperazone.

The initial water/acetone/sodium cefoperazone solution may be prepared by combining appropriate amounts of a slurry of cefoperazone free acid in acetone with an aqueous solution containing about one equivalent of a base selected from sodium bicarbonate, sodium carbonate and sodium 2-ethyl hexanoate.

The highly crystalline product may be separated by filtration or centrifugation and dried under vacuum (0.1 to 10 mm Hg) at about 25°C.

Highly crystalline sodium cefoperazone may be prepared by the controlled staged addition of acetone to an initial water/acetone/sodium cefoperazone solution of the composition 1.0-1.5 parts of water by volume, 2.0-5.0 parts of acetone by volume, and 1 part of sodium cefoperazone by weight. The aforementioned initial sodium cefoperazone solution is preferably formed in situ by combining appropriate amounts of a slurry of cefoperazone free acid in acetone with an aqueous solution of about one equivalent of a basic sodium salt compound, selected from the group consisting of sodium bicarbonate, sodium carbonate, and sodium 2-ethylhexanoate.

Acetone is added to the initial aqueous acetone solution of sodium cefoperazone until the water

content is reduced to 14-17% of the acetone volume at a temperature of 5-25°C, with a preferred temperature range of 18-25°C, producing a ratio of water/acetone/sodium cefoperazone solution of 1.0-1.5, parts of water by volume, 7.0-12.0 parts of acetone by volume, and 1 part of sodium cefoperazone by weight. The solution is then stirred until a haze develops, and stirring continued until a thick slurry has formed. Further acetone is then added, with stirring in the aforementioned temperature range until a final water content of 3-5% of the acetone level is obtained. The resulting crystals of sodium cefoperazone can be collected by conventional means, preferably by centrifugation or vacuum filtration and, if desired washed with available organic solvent, preferably 3% water/acetone solution, then with acetone or ethanol, and dried. The product is preferably dried at about 25-50°C, preferably under a vacuum of about 0.1 to 10 mm Hg, for about 1 to 20 hours.

The process of the present invention allows for the formation of highly crystalline sodium cefoperazone. By highly crystalline is meant a crystalline product that is substantially free of amorphous material. The process of the present invention also results in highly crystalline sodium cefoperazone which is essentially free of residual organic solvents, without requiring extraordinary drying conditions to reduce the amount of organic solvent to a range acceptable for human use.

Sodium cefoperazone is a broad spectrum antibiotic useful in treating bacterial infections in humans. The crystalline sodium cefoperazone produced by the process of this invention is used in the same manner as the amorphous product described in the art including British

Patent Specifications 1,508,071 and U.S. Patent
4,087,424. The highly crystalline sodium cefoperazone
produced by the present process is more stable,
less subject to undesirable decomposition and
5 more conveniently handled and incorporated in
pharmaceutical dosage forms than the amorphous
material.

The present invention is illustrated by the
following examples. It will, however, be
10 understood that the invention is not limited to
the specific details and conditions of these
examples.

Example I

10g. of partially crystalline sodium cefoperazone was dissolved in 15 ml. of water at a temperature of 20-25°C. To the stirred solution 106 ml of acetone was added at a temperature of 20-25°C , resulting in a slight haze. The hazy solution was stirred at 18-21°C until a thick slurry developed. After the thick slurry developed 325 ml of acetone was added over 2 hours. The final water content was measured at 3-4% of acetone content. Stirring was continued for 5 hours at 20-25°C, and the resulting crystals of sodium cefoperazone were collected by vacuum filtration, 8.9g. yield.

Example II

A slurry of 25g of cefoperazone free acid in 75 ml. acetone at 20-25°C was treated with a solution of 3.08g. sodium bicarbonate in 37.5 ml. of water with stirring to adjust the pH to 6.5-6.8 at 20-25°C. The resulting solution was clarified and 170 ml. of acetone was added over a half hour at 20-25°C until a slight haze resulted. The hazy solution was stirred at 20-25°C for about 2 hours until a thick slurry developed. 640 ml. of acetone was then added over 2 hours, maintaining the temperature of 20-25°C. Stirring continued for 5 hours at 20-25°C and the crystals were collected by vacuum filtration, 21.5g. yield.

CLAIMS

1. A process for preparing highly crystalline sodium cefoperazone which comprises the steps of (a) combining a water/acetone/sodium cefoperazone solution containing 1-1.5 parts of water by volume, 2.0-5.0 parts of acetone by volume, and 1 part of sodium cefoperazone by weight with sufficient acetone to provide a water/acetone solution containing from about 14% to about 17% (v/v) water based on acetone level at a temperature of about 5-25°C; (b) adding sufficient acetone to the resulting slurry at said temperature to provide a water/acetone solution containing from about 3% to 5% water based on acetone level; and (c) separating the resulting crystalline sodium cefoperazone from said slurry.

2. The process of claim 1 wherein said temperature is 18-25°C.

3. The process of claim 1, wherein said water/acetone/sodium cefoperazone solution is formed in situ by combining a slurry of cefoperazone free acid in acetone with an aqueous solution containing about one equivalent of a base selected from the group consisting of sodium bicarbonate, sodium carbonate and sodium 2-ethylhexanoate.



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 7)
A	DE-A-2 752 443 (E. LILLY & CO.) * Complete document *	1	C 07 D 501/24 // A 61 K 31/545
A	DE-A-2 600 880 (TOYAMA CHEMICAL CO.) * Page 12, lines 17-20; examples *	1	
D,A	GB-A-1 508 071 (TOYAMA CHEMICAL CO.)		
D,A	US-A-4 087 424 (TOYAMA CHEMICAL CO.)		
A	Chemical Abstracts vol. 92, no. 18, 5 May 1980, Columbus, Ohio, USA I. SAIKAWA et al. "Studies on beta-lactam antibiotics for medicinal purpose. X. Stability and degradation pattern of sodium 7-[D(-)-alpha-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-alpha-(4-hydroxyphenyl)acetamido]-3-[(1-methyl-1H-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylate (T-1551) in aqueous solution", page 396, column 2, abstract no. 152998u & Yakugaku Zasshi, vol. 99, no. 12, 1979, pages 1207-1218		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 7)
			C 07 D 501/24
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 09-04-1984	Examiner PHILLIPS N.G.A.
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



European Patent
Office

EUROPEAN SEARCH REPORT

0118196

Application number

EP 84 30 0616

Page 2

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
P, A	Chemical Abstracts vol. 98, no. 14, 4 April 1983, Columbus, Ohio, USA UNITED STATES FOOD AND DRUG ADMINISTRATION "Antibiotic drugs; sterile cefoperazone sodium", column 1, abstract no. 113578m & Fed. Regist., vol. 48, no. 5, 1983, pages 788-791 -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 7)
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 09-04-1984	Examiner PHILLIPS N.G.A.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	